Remarks/Arguments

Claims 44-46 and 49-51 are pending in this application and are rejected on various grounds. The rejection to the presently pending claims are respectfully traversed.

Priority

The Examiner granted priority to the PCT/US00/04414 Application, filed February 22, 2000, for the instant application but maintained his objection to granting priority based on International application PCT/US98/18824, filed on 10 September, 1998 indicating that "the claimed subject matter is not supported in the manner provided by 35 U.S.C. 112, first paragraph" in the earlier application. Applicants submit that they are entitled to priority of the earlier filed PCT/US98/18824, filed on 10 September, 1998, which discloses the "gene amplification assay" at least for the same reasons as for the granting of priority to Application PCT/US00/04414, filed February 22, 2000.

Further, Applicants discuss below the reasons why the gene amplification assay provides adequate support for utility of PRO317 polypeptides and respectfully traverse the rejections.

The Examiner asserts: (1) using Pennica that, one of skill in the art would have a legitimate basis to doubt the utility of PRO317 polypeptide because they would not know if the expression of PRO317 would be upregulated, soon-regulated, or unchanged in cancer; (2) that there is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein; and (3) that no information is provided in the gene amplification data regarding the level of expression, activity, or role in cancer of the PRO317 polypeptide.

Applicants respectfully traverse these rejections for the reasons set forth below.

Arguments

Regarding Pennica, Applicants respectfully maintain that Pennica teaches nothing regarding a lack of correlation of DNA and protein, in genes in general. The Utility Guidelines requires that for utility, it is **more likely than not** that a correlation exist between protein expression and gene amplification, in general. Applicants respectfully submit that Pennica's

teachings alone does not impart such a generalized teaching and thus, Pennica cannot be used against the Applicant to base a utility rejection.

Secondly, the Examiner rejects statements in Dr. Polakis' declaration and requests evidentiary support for the same. Applicants reproduce below, the entire paragraph with the relevant statement from Dr. Polakis' declaration so that the statement in question can be viewed in context:

> "Based upon my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4-5 above and my knowledge of the relevant scientific literature, it is my considered scientific opinion that **for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell.** In fact, it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. **While there have been published reports of genes for which such a correlation does not exist, it is my opinion that such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein"** (emphasis added).

Applicants further respectfully draw the Examiner's attention to the Utility Examination Guidelines, Part IIB, 66 Fed. Reg. 1098 (2001) which states that, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered". The statement in question from Dr. Polakis, an expert in the field, should be viewed in context of the evidentiary support (mRNA data for human genes) that he refers to, and upon which he bases his viewpoint. As Dr. Polakis himself clearly acknowledges, exceptions to the central dogma exist, and he qualifies this statement in his declaration by saying: "(w)hile there have been published reports of genes for which such a correlation does not exist, it is my opinion that such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." Applicants submit that Dr. Polakis' statements would be considered reasonable and accurate by

one skilled in the art, as required by the Utility guidelines, hence the Examiner's request for evidentiary support is improper.

Further, the Examiner uses Haynes and Hancock as evidence to show that Dr. Polakis' statement is not absolutely true. Applicants respectfully disagree with the Examiner conclusion that these references contradict Dr. Polakis' declaration. Applicants respectfully point out that, for example, in the Haynes reference, Haynes found that "**there was a general trend** but no strong correlation between protein [expression] and transcript levels" (Emphasis added). Haynes studied 80 *yeast* proteins to show that "protein levels cannot be **accurately** predicted from the level of the corresponding mRNA transcript" (Emphasis added) (see page 1863, paragraph 2.1, last line). That is, Haynes recognized that while there was a general trend of increased protein expression with increased mRNA levels, **the Haynes reference teaches that protein levels (i.e. protein amounts) cannot accurately be predicted from mRNA levels or amounts**, which is not the same as "no correlation between protein and mRNA". For example, even in Figure 1, Hayes shows that there was a *general* positive correlation between mRNA and protein amongst **most** of the 80 yeast proteins even though the correlation is "not strictly linear" thereby not enabling one to **accurately predict** protein levels from mRNA levels. In fact, a careful look at Figure 1 of Haynes indicates that few data points deviated or scattered away from the expected normal or showed a lack of correlation between mRNA: protein levels. Thus, contrary to the Examiner's position, the Haynes data actually supports Polakis' statement that, in general, a positive correlation exists between mRNA and protein levels (even though the correlation may not be linear and hence, the data cannot be used to accurately predict protein levels or amounts). The Haynes data in fact, meets the "more likely than not" utility standard since it studied **80 proteins** and showed "a general positive trend" or increase in protein levels for most of the 80 proteins with corresponding mRNA increases. Therefore, Applicants submit that in fact, support the Polakis' declaration and that the Examiner's rejection is based on a misrepresentation of the scientific data presented in Haynes *et al.*

Further, Applicants submit that the Hancock reference cited by the Examiner does not provide evidence that Dr. Polakis' statements are not absolutely true. Hancock discusses the need for high-quality biomarkers in the genomics and proteomics era and the need for a "consensus-building process" and "consolidation of different lists of biomarkers". While the editorial

indicates that the markers generated by proteomics are not always consistent with markers identified by expression profiling, which possibly reflects methodological differences between expression and proteomic studies, the statements in the editorial by no means provide evidence that Dr. Polakis' statements are not absolutely true. In fact, the statements in the editorial indicate the importance for proteomics (and protein markers generated thereof) in the third paragraph: "I think many people in the proteomics community would agree that federal granting agencies *should be enticed* to continue investments in basic proteomics technology." If anything, Hancock provides evidence that **biomarkers like PRO317 are useful**, and in fact desirable, provided there is a push towards a consolidated list of biomarkers (which is outside the scope of the utility requirement). Thus, Applicants respectfully point out that the Hancock reference in fact supports utility for protein markers despite seeming discrepancies between expression and proteomic studies.

Applicants also respectfully submit that Applicants have asserted utility for PRO317 polypeptides based on gene amplification of the DNA encoding polypeptide PRO317 in 14 lung tumors and 6 colon tumors. Again, based on the utility standards and the discussions presented above, a person of skill in the art would reasonably accept that based on the DNA amplification for the PRO317 nucleic acid, PRO317 protein levels would also increase.

In conclusion, the Examiner has not shown that a lack of correlation between gene amplification and polypeptide over-expression, **is typical** based on references Pennica, Haynes or Hancock. None of the cited references showed that it is **more likely than not** that the encoded protein will not be expressed at an elevated level when the gene is amplified. By contrast, in fact Haynes *et al.*, showed that **most genes** in the 80 gene studied showed a correlation between increased mRNA **and** increased protein levels in general, even if accurate prediction of protein levels (amounts) from mRNA levels was not possible. Hancock emphasized the need and the use of protein biomarkers generated through proteomics. Since the standard for utility is not one of absolute certainty, but rather "a more likely than not" standard; that is, that a person of skill in the art reasonably accept that for a given DNA increase, protein levels would "more likely than not" increase as well, Applicants submit that by presenting the gene amplification data for the PRO317 gene, they have adequately met the utility standard for the protein as well. Thus,

Applicants respectfully maintain that a *prima facie* showing of lack of utility has not been made in this instance.

Applicants further submit that the PRO317 proteins have utility in the diagnosis of cancer and thus, one of skill in the art would know exactly how to make and use these molecules for the diagnosis of cancer. The gene amplification disclosure does provide "specific benefit in the currently available form." Contrary to the Examiner's position, one skilled in the art would know how to use the claimed polypeptides for the diagnosis of lung or colon cancer, which is a specific utlity. Accordingly, PCT/US98/18824, filed on 10 September, 1998 also has utility and Applicants believe they are at least entitled to a priority date of **10 September, 1998**.

Accordingly, the present 35 U.S.C. §101 and §112, first paragraph utility rejections should be withdrawn.

Claim Rejections – 35 USC § 102

Claims 44-47, 49-51 are rejected under 35 U.S.C.§ 102 (a) allegedly as being anticipated by Ruben (publication date, February 25, 1999).

Based on the discussions on utility and priority above, Applicants believe that they are at entitled to an effective filing date of at least September 10. 1998 for this application. Since Ruben et al. is dated after this effective filing date, it is not prior art under 102(a) and therefore, this rejection should be withdrawn.

Information Disclosure Statement

Applicants will submit an IDS in compliance with USPTO rules shortly.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C17). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: March 21, 2005

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